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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte ANJA PENGER, REIMUND SPRENGER, and ULRICH BRINKMANN[1]

Appeal 2015-007994
Application 12/880,001
Technology Center 1600

Before ERIC B. GRIMES, JEFFREY N. FREDMAN, and ULRIKE W. JENKS, *Administrative Patent Judges.*

JENKS, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims directed to a method of determining if a subject is at risk of increased metabolism of a CYP2C8 substrate. The Examiner rejects the claims as indefinite, lacking descriptive support, lacking enablement, as well as being directed to patent ineligible subject matter. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

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[1] According to Appellants, the real party in interest is Transgenomic, Inc. (App. Br. 2.)

STATEMENT OF THE CASE

Claims 29 and 42–56 are on appeal[2], and a copy of the claims under consideration can be found in the Appellants' response filed April 3, 2013. Claim 42 is representative of the claims on appeal, and reads as follows:

> 42. A method for treating a human subject at risk for increased metabolism of a CYP2C8 substrate comprising the steps of:
>
> (a) detecting in a CYP2C8 polynucleotide in the genome of the human subject at least one copy of a G at the position corresponding to position 1668 of SEQ ID NO: 400;
>
> (b) identifying the human subject having at least one copy of a G at said position as being at risk for increased metabolism of the CYP2C8 substrate relative to the metabolism of the CYP2C8 substrate of a human subject having two copies of a T at said position; and
>
> (c) treating the human subject identified as being at risk for increased metabolism of the CYP2C8 substrate with an individualized therapy, wherein the individualized therapy is different from a conventional CYP2C8 substrate therapy for a human subject having two copies of a T at said position.

The following grounds of rejection are before us for review:

I. claims 29, 42–50, 52, 54, and 56 under 35 U.S.C. § 112, second paragraph, as being indefinite;

II. claims 42–50 and 54–56 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement in that they contain new matter;

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[2] The Examiner notes that "the after final amendment of November 21, 2014 has not been entered (see the Advisory action mailed December 19, 2014, particularly at Box 7). The claims on appeal are thus the finally rejected claims (claim set of April 3, 2013)." Ans. 12. Specifically, it is noted that claims 44 and 56 as they appear in the Claims Appendix of the Appeal Brief do not correspond to the claims under appeal. *Id.*

III. claims 42–50, 54, and 56 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement; and

IV. claims 29, 42–49, 51–53, and 56 under 35 U.S.C. § 101[3] as being directed to patent ineligible subject matter.

I Indefiniteness

Claim 52

Claim 52 recites the limitation of "a polynucleotide that specifically hybridizes to a CYP2C8 polynucleotide comprising a G at position 1668 of SEQ ID NO: 400." With respect to this claim, the Examiner's position is that "[n]either the specification nor the prior art provide a limiting definition of the term 'specifically hybridizes,' and it is thus not clear what types of polynucleotides are embraced by (and excluded from) claim 52." Final Act. 5. As written, the claims "encompass any 'use' in 'detecting' of a polynucleotide as recited in claim 52; there is no requirement in the claim for any type of allele-specific hybridization based assay, for a probe/primer that shares any particular structure with the recited polynucleotide, etc." Ans. 4.

Appellants contend that it was known in the art to design probes "that hybridize to one form of a biallelic marker and not to the other." Brief 8.

We find that Appellants have the better position. According to the Specification:

> The term "stringent hybridization conditions" is well known in the art; see, for example, Sambrook et al., 'Molecular Cloning, A Laboratory Manual' second ed., CSH Press, Cold Spring

[3] The Examiner withdrew the 35 U.S.C. § 101 rejections with respect to claims 50, 54, and 55. Answer 2.

> Harbor, 1989; "Nucleic Acid Hybridisation, A Practical Approach", Hames and Higgins eds., IRL Press, Oxford, 1985.

Spec. 30.

We understand the Examiner's rejection is directed at the possibility that the claims may encompass nucleic acid probes that do not necessarily overlap the particular position 1668 of SEQ ID NO: 400. We are not persuaded by the Examiner's rationale. Here, the Specification directs us to generic references that discuss cloning and primer selection generally. These references in conjunction with knowledge of the 2097 bases that make up SEQ ID NO: 400 as disclosed in the Specification, in addition to the knowledge of the particular mutation position 1668, would lead one of ordinary skill to design a probe that targets the area encompassing position 1668 in order to distinguish mutants at that location. The preponderance of evidence of record does not support the Examiner's position that the claim 52 is indefinite.

Claims 42–46 and 49

Claim 42 recites "individualized therapy, wherein the individualized therapy is different from a conventional CYP2C8 substrate therapy for a human subject having two copies of a T at said position." The Examiner's position is that claim 42 is indefinite because "the specification does not teach what might constitute an 'individualized therapy as specified in the claims, and particularly does not teach what would be considered conventional/different from conventional with respect to 'a human subject having two copies of a T' at the claimed position." Final Act. 5. "[T]he claims actually require 'treating' a subject with a particular type of 'individualized therapy' relative to that which is 'conventional . . . for a

human subject having' a specific CYP2C8 genotype." Answer 14. With respect to claim 44 the Examiner finds that "[t]he specification does not make clear what would/would not be considered a 'conventional' dose of such a substrate and/or a dose that is 'different from a conventional dose.'" Final Act. 6. In other words, the Examiner finds that the "required steps of treating/selecting/administering were not disclosed in the application as filed." Answer 14.

Appellants contend that the Specification shows that individuals have a different enzyme activity based on the presence or absence of G at position 1668 in SEQ ID NO: 400. *See* Brief 9. Appellants contend that "drugs that are CYP2C8 substrates are known, as are the common indications that are treated by those drugs. It is logical to conclude that there are conventional doses and regimens for each drug and indication." Brief 10.

We are not persuaded. Even with the understanding that allelic variants process their substrates at different rates, this does not clarify what is encompassed by "conventional therapies." Because "conventional therapies" associated with CYP2C8 are neither disclosed in the Specification nor readily understood from the art generally, we agree with the Examiner's position that the metes and bounds of these claims is not clear. Accordingly, we affirm the Examiner's rejection of claims 42–46 and 49 as being indefinite.

Claim 46

The Examiner finds that the claim lacks antecedent basis for the limitation 'the xenobiotic CYP2C8 substrate.'" Final Act. 6.

Appellants do not identify any error in the Examiner's indefiniteness rejection. We therefore summarily affirm the indefiniteness rejection based upon the Examiner's explanation and reasoning. *Id.*

Claims 47, 48, and 56

The Examiner finds that the claims are indefinite because the Specification does not disclose "the types of dosages/dosage regimens that are embraced by (and excluded from) the claims." Final Act. 6.

Appellants contend that the Specification shows that individuals have a different enzyme activity based on the presence or absence of G at position 1668 in SEQ ID NO: 400. *See* Brief 11. Appellants contend that "drugs that are CYP2C8 substrates are known, as are the common indications that are treated by those drugs. It is logical to conclude that there are conventional doses and regimens for each drug and indication." *Id.* at 10.

We are not persuaded. Even with the understanding that allelic variants process their substrates at different rates, this does not clarify what is encompassed by "conventional dosage regimen." Because conventional dosages of CYP2C8 substrates are neither disclosed in the Specification nor readily understood from the art generally, we agree with the Examiner's position that the metes and bounds of these claims are not clear. Accordingly, we affirm the Examiner's rejection of claims 47, 48, and 56 as being indefinite.

Claims 50, 54, and 56

The Examiner finds that the claims are indefinite because "defining the dosages as 'different' from one another does not make clear what is actually embraced by the claims." Final Act. 8. The Examiner finds that the claims are indefinite because it is unclear as to "what actually constitutes a

first and second dosage embraced" by the claims. *Id.* "Additionally (and as discussed in the original rejection), the claims are directed to a method of treating a single human subject, and thus would require administering either the first or second dosage referenced in claim 50 (but not both)." Ans. 11.

Appellants contend that the Specification shows that individuals can have different enzyme activity based genotype of CYP2C8. *See* Brief 12. Appellants contend that "the individual with at least one G at position 1668 will likely receive a different dosage regimen than the individuals that are homozygous T at position 1668, for that substrate to be effective, i.e., the first and second dosage regimens are different." *Id.*

We are not persuaded. Even with the understanding that allelic variants process their substrates at different rates, this does not clarify "what might constitute an appropriate dosage regimen with respect to either type of individual specified in the claim." Ans. 11. Because therapies associated with CYP2C8 are neither disclosed in the Specification nor readily understood from the art generally, we agree with the Examiner's position that the metes and bounds of these claims are not clear. Accordingly, we affirm the Examiner's rejection of claims 50, 54, and 56 as being indefinite.

II. New Matter

The Examiner's position is that the originally filed "specification does not disclose what might constitute an 'individualized therapy' as specified in the claims, and particularly does not teach what would be considered conventional/different from conventional with respect to 'a human subject having two copies of a T' at the claimed position." Final Act. 9, *see also id.* at 11. "[T]he specification as filed [also] does not disclose what might

constitute a 'dosage regimen is different from a conventional dosage regimen of the xenobiotic CYP2C8 substrate for a human subject having two copies of a T at said position.'" Final Act. 11. Therapies directed at the use "of 'first' and 'second' dosages set forth in the claims [also] lack basis in the original application." *Id.* at 12. The claims "embrace administering any non CYP2C8 substrate to a subject with one particular genotype and administering any xenobiotic CYP2C8 substrate to a subject having a different particular genotype, [this too was] not disclosed in the application as filed." *Id.* at 13. Because the claimed subject matter identified by the Examiner does not find support in the original application the claims are rejected as containing new matter.

We have reviewed, but are not persuaded by, Appellants' contention that the Specification provides sufficient descriptive support for the invention as presently claimed including the recited therapies. *See* Brief 13–16. Appellants contend that they need only supply detail of those elements that are "new and not conventional." *Id.* at 15. We agree with the Examiner that the as-filed the Specification does not provide sufficient description of the claim limitations of "individualized" and "conventional" therapies.

Appellants contend that "[t]he concept of individualized therapies (e.g., personalized medicine) based on genotyping was recognized by the art." Br. 15. "In the context of population variability with regard to drug therapy, pharmacogenomics has been proposed as a tool useful in the identification and selection of patients which can respond to a particular drug without side effects." Spec. 11; Brief 13. Specifically, the Specification explains that "suitable individual therapy can be designed based on the knowledge of the individual genetic makeup of a subject with

respect to the polynucleotides of the invention and improved therapeutics can be developed." Spec. 13–14.

A showing that the concept of individual therapy is known and recognized in the art is not sufficient to establish that the Specification contains a description of the subject matter as claimed. As explained by the Examiner "the claims actually require 'treating' a subject with a particular type of 'individualized therapy' relative to that which is 'conventional. . . for a human subject having' a specific CYP2C8 genotype." Answer 14. It is "[t]hese required steps of treating/selecting/administering [that] were not disclosed in the application as filed." *Id.*

We agree with the Examiner that a showing "that certain therapies were known to be 'conventional' in a subject having one genotype with respect to a previously unknown variant is not persuasive." Answer 15. In other words, showing that such individualized therapy has been established for a different gene variant has no bearing on what is disclosed in the Specification with respect to CYP2C8. It is the lack of description in the Specification of therapies associated CYP2C8 that is the basis for the new matter rejection. The presently claimed treatment for different CYP2C8 genotypes is not disclosed. Establishing that it is possible to test substrates is not sufficient to establish treatment for the subjects. "[I]t is the specification itself that must demonstrate possession. And while the description requirement does not demand any particular form of disclosure, . . . or that the specification recite the claimed invention *in haec verba*, a description that merely renders the invention obvious does not satisfy the requirement." *Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co.,* 598 F.3d 1336, 1352 (2010).

The preponderance of the evidence of record supports the Examiner's conclusion that the Specification does not disclose treatment regimens and therefore adding limitations to "individualized therapy" is new matter. We thus affirm the rejection of claims 42–50 and 54–56 under 35 U.S.C. § 112(a) as containing new matter.

III. Enablement

The Examiner rejects claims 42–50, 54, and 56 as failing to comply with the enablement requirement of 35 U.S.C. 112, first paragraph. Final Act. 13–15. "The specification is silent with regard to what types of therapies, dosages, etc., are actually required by the claims (and this information is not provided in the claims themselves)." Final Act. 14. "[N]o quantity of experimentation would be sufficient to enable the use of applicant's claims." *Id.* at 15. "[W]hile the specification is enabling with regard to the use of the 'detecting' of the claims in a variety of ways, it is not enabling with regard to methods requiring the specific treating/administering/selecting/etc. steps of the claimed invention." Answer 17.

We find that Appellants have the better position. Appellants contend that is was known in the art "that certain polymorphisms can affect the toxicity of drugs or the half-life of a drug with the result that a much lower dose may be required in certain subpopulations." Brief 16. "The enablement requirement is often more indulgent than the written description requirement. The Specification need not explicitly teach those in the art to make and use the invention; the requirement is satisfied if, given what they already know, the Specification teaches those in the art enough that they can

make and use the invention without 'undue experimentation.'" *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1334 (Fed. Cir. 2003).

Here, the art establishes that genetic polymorphisms in the human CYP2C subfamily have been shown to affect the metabolism of a variety of drugs. Brief 16. Goldstein[4] classifies patients into poor drug metabolizers and efficient drug metabolizers depending on their genetic makeup, so the drug dose can be adjusted so that toxic levels do not accumulate. Goldstein explains that "the clinical consequences of these rarer polymorphisms can be severe. Severe and life-threatening bleeding episodes have been reported in CYP2C9 PMs [(poor metabolizers)] exposed to warfarin." Goldstein, Abstract. As pointed out by Appellants, "[t]he specification discloses that individuals with at least one G at position 1668 have increased CYP2C8 substrate metabolizing activity (IM/EM) relative to individuals that are homozygous T at position 1668 (they have reduced CYP2C8 substrate metabolizing activity (PM))." Brief 16. The Specification also provides a list of known substrates for CYP2C8. *See* Spec. 2. We agree with Appellants' position that, based on the combination of what is known in the art with respect to other CYP2C polymorphisms in conjunction with what is disclosed in the Specification, one of skill in the art would know "to monitor patients such as those with at least one G at position 1668, that are administered a drug that may be metabolized by CYP2C8, or to adjust the dose or dosages of that drug so that the treatment will be more efficacious." Brief 16–17. "That *some* experimentation may be required is not fatal; the

[4] Goldstein, *Clinical relevance of genetic polymorphisms in the human CYP2C subfamily*, 52 Br. J. Clin. Pharmacol. 349–355 (2001).

issue is whether the amount of experimentation required is 'undue.'" *In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991) (emphasis in original).

In sum, as we are not persuaded, for the reasons discussed, that the Examiner has adequately established that the claims are not enabled for the recited treating/administering/selecting/etc. steps as claimed. Accordingly we reverse the rejection of claims 42–50, 54, and 56 under 35 U.S.C. § 112, first paragraph, as not being enabled.

IV. Claims Directed to Patent Ineligible Subject Matter

The Examiner has rejected claims 29, 42–49, 51–53, and 56 on appeal as directed to patent-ineligible subject matter. The Examiner finds that the claims are "not directed to patent eligible subject matter . . . [because they are] directed to a law of nature/natural principle." Final Act. 15. The Examiner analyzes the claims based on the USPTO's guidance on subject matter eligibility (*id.* at 15–18) and concludes that "the claims encompass general categories of well-known, conventional methodologies, and thus do not add any elements/steps that amount to significantly more than a natural principle." *Id.* at 16. "The claim[s] lack[] any active steps related to detecting/determining the genotype in question (which steps might result in the claim amounting to 'significantly more' than a natural principle)." *Id.* at 18.

Appellants do not contest that "[t]he occurrence of genetic variation, e.g., in a CYP2C8 gene, is a naturally occurring phenomenon." Brief 18. With respect to the independent claims Appellants contend that the claimed subject matter "is significantly more than the exception itself and has meaningful limitations beyond generally linking the use of the judicial

exception to a particular technological environment." Brief 19, *see* 20–23. Appellants contend that "by identifying a certain specific genetic variation at a particular position in a CYP2C8 ***gene relative to a different genetic composition*** at that position, [each independent claim] is directed to subject matter that is more than well-understood, routine or conventional in the relevant art." Brief 19, *see* 20–23.

We agree with the Examiner that the claims are directed to a patent-ineligible method for the reasons set out in the Final Action mailed December 30, 2013 and Answer which we adopt and incorporate herein by reference. We provide the following additional comment to argument set forth in the Appeal Brief. In *Mayo Collaborative Services v. Prometheus Labs., Inc.*, 132 S. Ct 1289 (2012), the Court considered a claimed method that required administering a drug, determining the level of a metabolite of the drug in the subject, and using certain thresholds of metabolite level to indicate a need to increase or decrease dosage of the drug. *Id.* at 1295.

The Court noted that the claims "set forth laws of nature—namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm." *Id.* at 1296. The Court held that the dispositive question was: "do the patent claims add *enough* to their statements of the correlations to allow the processes they describe to qualify as patent-eligible processes that *apply* natural laws?" *Id.* at 1297.

The Court held that the claim's "administering" step, "determining" step, and "wherein" clauses did not transform the claim into a patentable application of a natural law, *id.* at 1297–98: "The upshot is that the three

steps simply tell doctors to gather data from which they may draw an inference in light of the correlations." *Id.* at 1298.

The Court's analysis in *Mayo* is directly applicable to any one of the independent claims 29, 42, 47, and 49, which only require detecting a nucleotide at the position corresponding to position 1668 of SEQ ID NO: 400. Just as in *Mayo*, the claims inform a relevant audience of a law of nature and "any additional steps consist of well-understood, routine, conventional activity already engaged in by the scientific community." *Id.* Thus, the claims are directed to a patent-ineligible natural phenomenon or law of nature.

Appellants argue that "by identifying a certain specific genetic variation at a particular position in a CYP2C8 ***gene relative to a different genetic composition*** at that position, [each independent claim] is directed to subject matter that is more than well-understood, routine or conventional in the relevant art." Brief 19, *see* 20–23.

This argument is unpersuasive. The detecting step of any one of claims 29, 42, 47, and 49 is directed to determining a specific genetic variation at a particular position in CYP2C8, namely determining the nucleotide at the position corresponding to position 1668 of SEQ ID NO: 400. This assay step is narrower than the one recited in the claimed method in *Mayo*, which encompassed "determin[ing] the level of the relevant metabolites in the blood, through whatever process the doctor or the laboratory wishes to use." *Mayo*, 132 S.Ct at 1297. We conclude, however, that this distinction does not make any one of claims 29, 42, 47, and 49 patent-eligible. The *Mayo* Court noted that "methods for determining metabolite levels were well known in the art. . . . Thus, this step tells

doctors to engage in well-understood, routine, conventional activity previously engaged in by scientists who work in the field." *Id.* at 1297–98.

The Court concluded: "Purely 'conventional or obvious' '[pre]-solution activity' is normally not sufficient to transform an unpatentable law of nature into a patent-eligible application of such a law." *Id.* at 1298, alteration in original. The same analysis applies here. Detecting the presence of a polynucleotide substitution at a particular location requires only conventional and routine assays. Appellants' Specification, in fact, acknowledges that "[t]he methods of the mutation analysis followed standard protocols and are described in detail in the Examples." Spec. 12. The "methods encompass for example haplotype analysis, single-strand conformation polymorphism analysis (SSCA), PCR and direct sequencing." Spec. 12–13. Thus, the inclusion of the detecting step in the claimed method does not transform the claim into a patent-eligible application of a law of nature.

For the reasons discussed above, we affirm the rejection of independent claims 29, 42, 47, and 49 under 35 U.S.C. § 101. Claims 43–46, 48, 51–53, and 56 fall with claim the independent claims. 37 C.F.R. § 41.37(c)(1)(iv).

SUMMARY

We affirm the rejection of claims 29, 42–50, 54, and 56 under 35 U.S.C. § 112, second paragraph, as being indefinite.

We reverse the rejection of claim 52 under 35 U.S.C. § 112, second paragraph, as being indefinite.

We affirm the rejection of claims 42–50 and 54–56 under 35 U.S.C. § 112, first paragraph, as containing new matter.

We reverse the rejection of claims 42–50, 54, and 56 under 35 U.S.C. § 112, first paragraph, as not being enabled.

We affirm the rejection of claims 29, 42–49, 51, 52, 53, and 56 under 35 U.S.C. § 101 as being directed to patent ineligible subject matter.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED